Remarks

To address the Examiner's objections to the claims, Applicants have amended claims to incorporate grammatical changes and inclusion of full name of an abbreviated term, as suggested by the Examiner. Applicants have cancelled claims 44, 51-62, 74-87, 91-97, and 101. Applicants have added new claims 187-213. Support for the new claims can be found in the specification, in part on page 9, lines 1-2. No new matter has been added.

Applicants gratefully acknowledge the Examiner's finding that claims 38, 41, 79, 82, and 84 are free of the prior art.

Priority

Applicants respectfully acknowledge the Examiner's placing the papers (United Kingdom 9908670.4 filed on 4/15/1999) submitted under 35 U.S. C. 119(a)-(d), of record in the file and Examiner's acknowledgment of priority to provisional 60/129,596 filed on 4/15/99.

Information Disclosure Statement

Applicants acknowledge Examiner's finding that the information disclosure statement filed on January 12, 2001 does not fully comply with the requirements of 37 CFR 1.98 and herewith file a substitute 1449 properly citing the journal articles indicated by the Examiner (C22, C26, and C28).

Claim Objections

The Examiner has rejected claims 11-13, 18-20, 37, 53-56, 59-61, 78, 82, and 92-94 because of informalities. Applicants have corrected the informalities in the claims and believe the claims to be in condition for allowance.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1, 8-13, 17-30, 51-62, 74-78, 91-97, and 101 under 35 U.S.C. 112 as being indefinite. Applicants have amended claim 101 to clarify its meaning. Applicants have amended dependent claims 8-13, 17-30, 36-43, 51-62, 74-85, 87, 91-97, and 101 to change the word "A" to the word "The" to point out which method is referred to in the claims.

Applicants have amended claims 36, 40, 77, and 81 to include "essential structural cooperative relationships of elements" as requested by the Examiner.

Applicants submit that the amendments fully address the Examiner's rejections and believe the claims to be in condition for allowance.

The Examiner states that the term "means" in claims 1, 17, 19, 44, 53, 58, 60, 86, 91, and 93 is a relative term and that the disclosure does not define the metes and bounds of the term. Applicants respectfully submit that the specification defines the phrase, "non-visual detection means" as "any means of detecting a signal which does not require visual inspection by the human eye" (page 5, lines 13-15). Exemplary non-visual detection means include multi-well plate readers, which are also known as microtiter plate readers and ELISA plate readers (page 6, lines 29-30); fluorescence activated scanning and sorting devices (FACS) and fluorescence activated nematode scanning and sorting device (FANS) (page 7, lines 14-20). Applicants submit that the meaning of the term "means" in the claims is clear based on the teaching in the specification and that one of ordinary skill in the art would be reasonably apprised of the scope of the invention. Therefore, Applicants have not amended claims 1, 17, 19, 44, 53, 58, 60, 86, 91, and 93 by substituting the term "device" for the term "means" as suggested by the Examiner.

In view of the foregoing amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 8-13, 17-30, 36, 40, 44, 51-62, 74-78, 81, 86. 91-97, and 101 under 35 U.S.C. §112 second paragraph.

Claim Rejections Under 35 U.S.C. §102

The Examiner has rejected claims 1, 8-11, 17-18, 23-30, 36-37, and 40 under 35 U.S.C. 102(b) as being anticipated by Rand et al. (Methods in Cell Biology, Vol. 48, 1995). According to the Examiner, Rand teaches combining compounds and *C. elegans* (wild type) in a method for studying the interaction of the two and further teaches that micro-titer plates or other multi-well plates are useful for experiments because they permit strains and/or drug concentrations to be tested in parallel. The Examiner further characterizes Rand as teaching that the experiment can take place in liquid medium or on agar plates, and that it is important to use synchronous populations to determine state-specific effects directly. In addition, the Examiner also states that Rand discusses using a quantitative assay for resistance sensitivity to the drug being tested. The

Examiner concludes that Rand anticipates the invention of claims 1, 8-11, 17-18, 23-30, 36-37, and 40.

Claims 1, 8-11, 17-18, 23-30, 36-37, and 40 are directed to a method of identifying chemical substances which have potential pharmacological activity using nematode worms. The method involves three steps:

a) dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate

b) contacting the nematode worms with a chemical substance

c) detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means.

Applicants respectfully traverse the rejection of claims 1, 8-11, 17-18, 23-30, 36-37, and 40 as anticipated by Rand for the reasons set forth below.

Rand et al. teaches compound-based studies of *C. elegans*, to characterize aspects of *C. elegans* biology and as a strategy for screening selective agents to isolated new drug-resistant or hypersensitive mutants and thereby identify genes with altered drug responses. In specific, Rand teaches the use of nematodes, the use of microtiter plates and synchronous populations of nematodes, and the use of a quantitative assessment, which they further describe as quantitation by behavioral testing and quantitation by measures of growth and development – each of which are described as quantitated using visual means including "visual determination of length" (Rand at page 198) and a "labor-intensive method of progeny counting" (Rand at page 199). Rand does not teach any non-visual method of detection within the meaning as defined within the present application.

The claimed invention is directed to methods that require a non-visual detection method. The application defines the phrase, "non-visual detection means" as "any means of detecting a signal which does not require visual inspection by the human eye" (page 5, lines 13-15). Exemplary non-visual detection means include multi-well plate readers, which are also known as microtiter plate readers and ELISA plate readers (page 6, lines 29-30); fluorescence activated scanning and sorting devices (FACS) and fluorescence activated nematode scanning and sorting device (FANS) (page 7, lines 14-20). The Rand reference does not teach a non-visual detection method. Accordingly, Rand does not anticipate claim 1 and the claims dependent thereon (claims 8-11, 17-18, 23-30, 36-37, and 40).

In addition to lacking elements of the independent claim 1, Rand et al., also lacks elements of the claims that depend from claim 1, which were also rejected by the Examiner under 102(b). Rand does not teach use of *C. briggsae* in assays, which is a limitation in claim 9, and does not teach detection of a change in a measurable property of a marker molecule, which is a limitation in claim 10 and 11. Rand also does not teach the use of a multi-well plate reader for detection, which is a limitation of claims 17 and 18, and does not teach dispensing substantially equal volumes of a homogeneous suspension of nematode worms into wells of a multi-well plate, which is a limitation of claim 23. Rand does not teach the use of hermaphrodite or male worms in an assay, which is a limitation of claim 29, and Rand does not teach the use of trangenic or humanized strains of nematodes, which are limitations of claim 30. In addition, Rand does not teach the use of a viscous solution for a homogenous suspension of nematodes, which is a limitation of claims 24-26, 36, 37, and 40. Accordingly, Rand does not anticipate dependent claims 9, 10-11, 17-18, 23-26, or 29-30, 36-37, or 40.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 8-11, 17-18, 23-30, 36-37, and 40 under 35 U.S.C. §102(b) as anticipated by Rand et al.

The Examiner has rejected claims 1, 8, 9, 23-30, 36-37, 40, 42, 44, 51-52, 74-78, 81, 83, and 85 under 35 U.S.C. §102(b) as being anticipated by Avery (J. Exp. Zoology, vol. 252:263-270, 1990). According to the Examiner, Avery teaches an assay that allows measurement of the pharynx-pumping rate in a population of worms suspended in a liquid medium by measuring their uptake of iron particles. The Examiner asserts that Avery also teaches that the assay is useful for measuring the effects of drugs on pumping, and that wild-type worms and hermaphrodites can be used in the assay. The Examiner concludes that Avery anticipates the invention of claims 1, 8, 9, 23-30, 36-37, 40, 42, 44, 51-52, 74-78, 81, 83, and 85.

Claims 1, 8, 9, 23-30, 36-37, 40, and 42 are directed to a method of identifying chemical substances that have potential pharmacological activity using nematode worms. The method involves three steps:

a) dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate

b) contacting the nematode worms with a chemical substance

c) detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means.

Claims 44, 51-52, 74-78, 81, 83, and 85 are directed to a method of identifying chemical substances that have potential pharmacological activity using nematode worms. The method involves three steps:

a) dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate

b) contacting the nematode worms with a sample of a chemical substance

c) detecting changes in the pharynx pumping rate of the nematode worms using non-visual detection means.

Applicants respectfully traverse the rejection of claims 1, 8, 9, 23-30, 36-37, 40, 42, 44, 51-52, 74-78, 81, 83, and 85 as anticipated by Avery for the reasons set forth below.

Avery teaches assays of drug effects in wild-type and hermaphroditic *C. elegans*, in which animals are suspended in liquid and their uptake of iron particles in the liquid is measured and quantitated, as a measure of pharynx pumping behaviour in the animals. Quantitation, as taught in Avery, involves allowing the worms to take up iron particles in the presence or absence of drug candidates, collecting and pelleting the animals, spreading the animals out on a microscope slide, and using polarized dark-field microscopy to hand count iron particles in the pharynxes and intestines of each worm carcass (Avery at page 264). Avery does not teach the use of dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means. Avery does teach measuring pharynx-pumping behavior, but does not teach doing so using any non-visual detection means.

Claim 1 is directed to methods that require dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means. Claim 44 is directed to methods that require dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and detecting changes in the pharynx pumping rate of the nematode worms using non-visual detection means. The Avery reference does not teach any of these limitations. Accordingly

Avery does not anticipate claim 1 and the claims dependent thereon (claims 8, 9, 23-30, 36-37, 40, 42, 44, 51-52, 74-78, 81, 83, and 85) and does not anticipate claim 44 and the claims dependent thereon (claims 51-52, 74-78, 81 and 85).

In addition to lacking elements of the dependent claims 1 and 44, Avery also lacks elements of the claims that depend from claim 1, which were also rejected by the Examiner under 102(b). Avery does not teach use of *C. briggsae* in assays, which is a limitation of claims 9 and 52 and does not teach dispensing substantially equal volumes of a homogeneous suspension of nematode worms into wells of a multi-well plate, which is a limitation of claim 23. Avery does not teach using worms that are synchronized in the same growth stage, which is a limitation of claims 27 and 74. Avery does not teach the specific use of eggs, L1 stage, L2 stage, L3 stage, adult worms or dauer worms, which are limitations of claims 28 and 75, and also does not teach specific use of male worms in an assay, which is a limitation of claims 29 and 76. Avery also does not teach the use of trangenic or humanized strains of nematodes, which are limitations of claim 30. In addition, Avery does not teach the use of a viscous solution for a homogenous suspension of nematodes, which is a limitation of claims 24-26, 36, 37, and 40. Avery does not teach the use of a water-soluble polymer in the liquid medium, which is a limitation of claims 40, 42, 77, 78, 81, and 83. Avery also does not teach an assay to identify chemical substances with insecticidal properties, which is a limitation of claim 85. Accordingly, Avery does not anticipate dependent claims 9, 23-30, 36-37, 40, 42, 52, 74-78, 81, 83, and 85.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 8, 9, 23-30, 36-37, 40, 42, 44, 51-52, 74-78, 81, 83, and 85 under 35 U.S.C. §102(b) as anticipated by Avery et al.

Claim Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 1, 8-11, 17-18, 23-30, 36-37, and 40 under 35 U.S.C. 103(a) as being unpatentable over Rand et al., taken with Leitch et al. (Antimicrobial Agents and Chemotherapy, Vol. 41:337-344, 1997). Claims 1, 8-11, 17-18, 23-30, 36-37, and 40 are described above in reference to the rejection of claims under 102(b). Applicants respectfully traverse the rejection.

According to the Examiner, the primary reference, Rand, teaches combining compounds and *C. elegans* in a method of studying the interaction of the two and Rand further teaches that micro-titer plates or other multi-well plates are useful in experiments because they permit many strains and/or drug concentrations to be tested in parallel. The Examiner also states that Rand teaches that the experiments can be done in liquid or on agar plates, synchronous populations can be used, and suggests the use of a quantitative assay for resistance/sensitivity to the drug being tested. The Examiner finds that Rand does not teach a method of identifying a chemical substance, which has potential pharmacological activity using worms, which method comprises the step of detecting a signal by detecting a change in a measurable property of a marker molecule, wherein the marker molecule is a fluorescent molecule. The Examiner characterizes the secondary reference, Leitch et al, as teaching the use of a fluorescent probe to assess the activity of a substance using confocal microscopy to "visualize the fluorescent probe calcein within infected cells of a parasite" (Paper mailed 2/14/02, page 9).

Applicants reiterate the description of the primary reference, Rand, as described above in reference to the rejection of claims under 102(b). Rand does not teach dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means. The deficiencies in the primary Rand reference are not cured by the teaching of the secondary Leitch reference.

The secondary reference, Leitch et al., is directed to methods for assessing drug compounds in mammalian cells (green monkey kidney cells) infected with *Encephalitozoon* Microsporidia. The method includes the visual detection of the fluorescent probe calcein through the use of confocal microscopy, which uses the eye to visually detect the fluorescent probe. This is in contrast to the non-visual detection methods of the invention in which, as defined in the specification, include, "any means of detecting a signal which does not require visual inspection by the human eye" (page 5, lines 13-15). The Leitch reference does not teach dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means. In addition, contrary to the Examiner's interpretation, Leitch does not teach visualization of a fluorescent probe within infected cells of a parasite, but rather teaches application of a

fluorescent probe to mammalian cells that are infected with a parasite. Leitch teaches that the probe is taken up by viable mammalian cells, but is not taken up by viable parasites. The presence of the probe in the viable mammalian cells permits the visual observation of the parameters of the mammalian cell as affected by the parasite, such as parasitiphorous vacuole organization or viability of various parasite stages. This use is in contrast with the teaching of the claimed invention, which involves application of a probe, not to a cell infected with an intracellular organism, but to a viable organism (a worm). The Leitch reference lacks teaching of applying a probe or marker to a living organism to detect or monitor phenotypic, physiological, behavioral, or biochemical changes in the living organism with non-visual detection means. As taught by Leitch, the probe only enters an organism (the parasite) when the organism is dead – and therefore can not be intended to indicate phenotypic, physiological, behavioral, or biochemical changes in function in the organism. Leitch teaches administration of a probe to a mammalian cell to assess the viability of an intracellular parasite following contact of the mammalian cell with candidate anti-parasitic agents. In addition, Leitch does not teach assessment or observation using a non-visual means.

To establish a *prima facie* showing of obviousness requires motivation, a reasonable expectation of success, and the prior art reference (or combination of references) must teach or suggest all the claimed limitations. The combination of the Rand and Leitch references does not meet these requirements because taken together the references do not provide motivation, teach, or suggest all the claimed limitations of the invention. Rand teaches visual observation via microscopy and video image recording and Leitch teaches visual observation with confocal microscopy. Neither reference teaches or suggests the use of any non-visual detection method. Therefore, the combination of these references would not result in the claimed invention and additionally, one would not be motivated, based on a combination of these references to utilize a non-visual detection method.

In addition, although the Leitch reference does teach a method of using a calcein probe, the method differs substantially from the use of such a probe in the claimed invention. The fact that Leitch teaches administering a probe to a mammalian cell to screen anti-parasitic drug candidates in no way teaches or suggests application of a similar method for use in the instant invention. This is especially apparent since the methods of the instant invention apply to a non-mammalian system and are fundamentally different to those of Leitch. The Examiner has not

provided any evidence that would suggest motivation to combine the teaching of Leitch with the teaching of Rand to arrive at the instant invention. The Examiner has merely disclosed isolated elements of the claimed invention without a specific teaching of how to go about the claimed invention (Smithkline Diagnostics v. Helena Laboratories, 859 F.2d 878 (Fed. Cir 1988), which is an impermissible use of hindsight and does not support a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 8-11, 17-18, 23-30, 36-37, and 40 under 35 U.S.C. §103(a) as anticipated by Rand in view of Leitch et al.

The Examiner has rejected claims 1, 8-11, 17-18, 23-30, 36-37, 44, 86, 87, 91-92, and 95-97 under 35 U.S.C. 103(a) as being unpatentable over Kerr et al. (West Coast Worm Meeting, Abstract 77, 1998) , taken with Rand. Applicants respectfully traverse the rejection.

Claims 1, 8-11, 17-18, 23-30, 36-37, and 44 are described above in reference to the rejection of claims under 102(b). Claims 86, 87, 91-92 and 95 are directed to a method of identifying chemical substance s which have potential pharmacological activity using nematode worms. The method involves three steps:

a) dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well plate;
b) contacting the nematode worms with a sample of a chemical substance
c) detecting changes in the intracellular levels of ions, metabolites or secondary messengers in cells of the nematode worms using non-visual means.

According to the Examiner, Kerr teaches imaging calcium transients in a subset of excitable cells in *C. elegans*, and does not "teach a method of identifying a chemical substance, which has potential pharmacological activity using nematodes worms placed in equal numbers in multi-well plates, which method comprises the step of detecting a signal indicating a biochemical change using non-visual detection device, multi-well plates and a liquid medium or agar medium" (Paper mailed 2/14/02, page 10).

According to the Examiner, the secondary reference, Rand, teaches combining compounds and *C. elegans* in a method of studying the interaction of the two and further teaches that micro-titer plates or other multi-well plates are useful in experiments because they permit many strains and/or drug concentrations to be tested in parallel. The Examiner also submits that

Rand teaches that the experiments can be done in liquid or on agar plates, suggests the use of synchronous populations, and suggests the use of a quantitative assay for resistance/sensitivity to the drug being tested. The Examiner finds that Rand does not teach a method of identifying a chemical substance, which has potential pharmacological activity using worms, which method comprises the step of detecting a signal by detecting a change in a measurable property of a marker molecule, wherein the marker molecule is a fluorescent molecule. The Examiner concludes that Rand's discussion of quantitative assays for resistance/sensitivity to the drug being tested, would, in the absence of evidence to the contrary, lead one of ordinary skill in the art to use a plate reader in the assessment of the drug effects. The Examiner also asserts that it would be obvious to one skilled in the art, absent evidence to the contrary, that when the worms are placed in a liquid medium, they would not stick to the plate.

The primary reference, Kerr, et al., is directed to methods for assessing electrical activity in *C. elegans* using genetically-encoded ratiometric fluorescent calcium sensors, which are visualized with two-photon confocal microscopy. Although the fluorescent calcium sensors are used to detect changes in the intracellular levels of ions, Kerr does not teach the use of any non-visual detection means to examine the electrical activity in the worms, or to examine phenotypic, physiological, behavioral, or biochemical changes in the nematode worms. Kerr also does not teach dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well plate. The teaching in the secondary references does not cure the deficiencies in the teachings of the Kerr reference.

Applicants reiterate the description of the secondary reference, Rand, as described above in reference to the rejection of claims under 102(b) and 103(a). Rand does not teach the use of dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means.

Applicants also respectfully submit that the Examiner's statement that "it would be obvious to one of ordinary skill that worms would not stick to the plate" is a conclusory statement for which the Examiner provides no evidence in support. It is also inconsistent with the findings by the Applicants. The specification of the instant disclosure teaches that worms sticking to the plate is a problem and that the problem is solved by the aspect of the invention that involves the addition of polymers to the liquid medium as described in the disclosure and

claims. Thus, in contrast to the conclusion of the Examiner, it would not be obvious that the worms would not stick to the plate, when in fact they do stick.

To establish a *prima facie* showing of obviousness requires motivation, a reasonable expectation of success, and the prior art reference (or combination of references) must teach or suggest all the claimed limitations. The combination of the Kerr and Rand references does not meet these requirements because together the references do not provide motivation, teach, or suggest all the claimed limitations of the invention. There is no teaching in either reference directed to detecting a signal using a non-visual detection means. Kerr teaches visual observation via confocal microscopy and Rand teaches visual observation via microscopy and video-image recording. Neither reference teaches or suggests the use of any non-visual detection method, therefore, the combination of the teaching in these references would not lead to the claimed invention and one would not be motivated, based on the combination of these references to utilize a non-visual detection method.

The Examiner's assertion that based on Rand, one of ordinary skill would use a plate reader to assess the drug effects on worms because a plate reader "is a standard piece of laboratory equipment" does not meet the evidentiary requirements for a *prima facie* case of obviousness. The fact that a piece of equipment may exist in a laboratory, does not serve as evidence of motivation to combine two references cited by the Examiner. The Examiner has merely disclosed isolated elements of the claimed invention without a specific teaching of how to go about the claimed invention (Smithkline Diagnostics v. Helena Laboratories, 859 F.2d 878 (Fed. Cir 1988), which is an impermissible use of hindsight and does not support a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 8-11, 17-18, 23-30, 36-37, 44, 86, 87, 91-92, and 95-97 under 35 U.S.C. 103(a) as being unpatentable over Kerr et al. in view of Rand.

The Examiner has rejected claims 1, 8-11, 17-20, 23-30, 36-37, and 39-40 under 35 U.S.C. 103(a) as being unpatentable over Rand, taken with Miwa et al. (U.S. Patent No. 4,444,981) in further view of applicants' own admission that a non-visual detection system is commercially available from UNION BIOMETRICA, INC. Applicants respectfully traverse the rejection.

Claims 1, 8-11, 17-20, 23-30, 36-37, and 40 are described above in reference to the rejection of claims under 102(b). Claim 39 is directed to a method of the invention in which the concentration of water-soluble polymer in the liquid medium is 0.3%.

According to the Examiner, the secondary reference, Rand, teaches combining compounds and *C. elegans* in a method of studying the interaction of the two and further teaches that micro-titer plates or other multi-well plates are useful in experiments because they permit many strains and/or drug concentrations to be tested in parallel. The Examiner also submits that Rand teaches that the experiments can be done in liquid or on agar plates, suggests the use of synchronous populations, and suggests the use of a quantitative assay for resistance/sensitivity to the drug being tested. The Examiner finds that Rand does not teach a method of identifying a chemical substance, which has potential pharmacological activity using worms, which method comprises the step of detecting a signal by detecting biochemical changes in the nematode worms using non-visual detection means, wherein the non-visual detection means is a FANS device. The Examiner concludes that Rand's discussion of quantitative assays for resistance/sensitivity to the drug being tested, would, in the absence of evidence to the contrary, lead one of ordinary skill in the art to use a plate reader in the assessment of the drug effects. The Examiner also asserts that it would be obvious to one skilled in the art, absent evidence to the contrary, that when the worms are placed in a liquid medium, they would not stick to the plate.

The Examiner states that Miwa suggests that the "chemical industry is producing novel chemical substance and research is being done to find new applications for known chemical substances and that in each case, it is desirable to establish a rapid method for testing substances" (Paper mailed 2/14/02, page 12).

The Examiner further asserts that one of ordinary skill in the art would combine the teaching of Rand with Miwa and would then view those teachings in combination with the existence of a FANS device, and would arrive at the claimed invention.

Applicants reiterate the description of the primary reference, Rand, as described above in reference to the rejection of claims under 102(b) and 103(a). Rand does not teach the use of dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means.

The deficiencies in the primary reference are not cured by the secondary reference or by Applicants' alleged admission of the existence of a FANS device.

The secondary reference, Miwa, suggests that a rapid method of testing toxicity of substances is desirable and teaches that the method discussed in Miwa is such a rapid method. Thus, there is no motivation to modify the Miwa teachings in the manner suggested by the Examiner. Miwa teaches a method of assessing chemical effects on nematodes that involves contacting nematode with a chemical and assessing the effect of the chemical by visual examination of a subsequent generation of nematodes. The reference does not teach detection using a non-visual detection means, does not teach placing equal numbers of nematodes in each well of a multi-well plate, and does not teach or suggest methods to detect a signal *in* the nematode(s) contacted with the chemical.

To establish a *prima facie* showing of obviousness requires motivation, a reasonable expectation of success, and the prior art reference (or combination of references) must teach or suggest all the claimed limitations. The combination of the Rand and Miwa references, in view of the existence of FANS device, does not meet these requirements because together the references do not provide motivation, teach, or suggest all the claimed limitations of the invention. There is no teaching in either Rand or Miwa that is directed to detecting a signal using a non-visual detection means. Rand teaches visual observation via microscopy and video image recording, and Miwa does not teach detection of signals of any kind in the worms in the assay, but rather teaches visual observation of offspring of the assay worms. Neither reference teaches or suggests the use of any non-visual detection method, therefore, the combination of the teaching in these references would not lead to the claimed invention and one would not be motivated, based on the combination of these references to utilize a non-visual detection method.

In addition, the Examiner's assertion that based on Rand, one of ordinary skill would use a plate reader to assess the drug effects on worms because a plate reader "is a standard piece of laboratory equipment" does not meet the evidentiary requirements for a *prima facie* case of obviousness. The fact that a piece of equipment may exist, be it a plate reader or a FANS device, does not serve as evidence of motivation to combine two references that do not teach any non-visual detection systems. The Examiner has merely disclosed isolated elements of the claimed invention without a specific teaching of how to go about the claimed invention (Smithkline

Diagnostics v. Helena Laboratories, 859 F.2d 878 (Fed. Cir 1988), which is an impermissible use of hindsight and does not support a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 8-11, 17-20, 23-30, 36-37, 39-40 under 35 U.S.C. 103(a) as being unpatentable over Rand in view of Miwa, taken with applicants' alleged admission that a FANS device is available.

The Examiner has rejected claims 1, 36-37, and 39 under 35 U.S.C. 103(a) as being unpatentable over Rand taken with Balan (J. Chem Ecology, 11:105-111, 1985). Applicants respectfully traverse the rejection.

Claims 1, 8-11, 17-20, 23-30, 36-37, and 40 are described above in reference to the rejection of claims under 102(b) and 103(a).

According to the Examiner the primary reference, Rand, teaches combining compounds and *C. elegans* in a method of studying the interaction of the two and further teaches that micro-titer plates or other multi-well plates are useful in experiments because they permit many strains and/or drug concentrations to be tested in parallel. The Examiner also submits that Rand teaches that the experiments can be done in liquid or on agar plates, and teaches what age the worms should be (Paper mailed 2/14/02, page 13). The Examiner finds that Rand does not teach a method of identifying a chemical substance, which has potential pharmacological activity using nematode worms, which method is performed in a liquid assay medium containing a water-soluble polymer at a concentration sufficient to increase the viscosity of the medium, wherein the concentration of water-soluble polymer in the liquid medium is 0.3%.

According to the Examiner, the Balan reference teaches a simple method for the experimental determination of minimal concentrations of chemical attractants by the nematode *Panagrellus ridivivus*. The Examiner also describes Balan as teaching the use of a 0.3% agar plate with the attractant and two similar control disks not containing the attractant. The Examiner also states that Balan teaches that this method could also be used with other nematodes and/or for the research of nematode repellant substances (Paper mailed 2/14/02, page 13).

Applicants reiterate the description of the primary reference, Rand, as described above in reference to the rejection of claims under 102(b) and 103(a). Rand does not teach the use of dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well

assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means. Rand also does not teach a method of identifying a chemical substance, which is performed in a liquid assay medium containing a water-soluble polymer at a concentration sufficient to increase the viscosity of the medium wherein the concentration of water-soluble polymer in the liquid medium is 0.3%. The deficiencies in the primary reference are not cured by the secondary reference.

The Balan reference teaches the use of 3% agar, which is a solid medium, in assays of the effect of chemical attractants on nematodes. The reference does not teach an assay performed in a liquid assay medium containing a water-soluble polymer at a concentration sufficient to increase the viscosity of the medium wherein the concentration of the water-soluble polymer in the liquid medium is 0.3%. The Balan reference also does not teach dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means.

To establish a *prima facie* showing of obviousness requires motivation, a reasonable expectation of success, and the prior art reference (or combination of references) must teach or suggest all the claimed limitations. Respectfully, the Examiner appears to have incorrectly interpreted the teaching in the Balan reference. Combining the teaching of the Balan reference, with the teaching of the Rand reference does not lead to the claimed invention, because several elements of the claimed invention are missing, namely, the steps involving dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate, detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means, and adding a polymer to increase the viscosity of the liquid medium wherein the concentration of the water-soluble polymer in the liquid medium is 0.3%. Based on these missing elements, a *prima facie* case of obviousness is not supported.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 36-37, and 39 U.S.C. 103(a) as being unpatentable over Rand in view of Balan.

The Examiner has rejected claims 1, 23-30, 36-37, 39, 40, 42, 44, 51-54, 58-62, 74-78, 80, and 85 under 35 U.S.C. 103(a) as being unpatentable over Avery taken with Miwa et al., in further view of applicants' own admission that a non-visual detection system is commercially available from UNION BIOMETRICA, INC. Applicants respectfully traverse the rejection.

Claims 1, 23-30, 36-37, 40, , 42, 44, 51-52, 56-57, 74-78, and 85 described above in reference to the rejection of claims under 102(b) and 103(a). Claims 53-54, 58-62 and 80 represent further limitations to claim 44, and include:

Claim 53: detecting changes in the pharynx pumping rate comprises contacting the nematode worms with a marker molecule which generates a signal when taken up by nematode worms and detecting the said signal using non-visual detection means

Claim 54: the marker molecule is a fluorescent molecule, a luminescent molecule, a colored molecule, a precursor of a fluorescent marker molecule, a precursor of a luminescent marker molecule or a precursor of a colored marker molecule

Claim 58: the non-visual detection means is a multi-well plate reader.

Claim 59: the multi-well plate reader performs luminescence, fluorescence or spectrophotometric detection.

Claim 60: the non-visual detection means is a FANS device.

Claim 61: the FANS device performs luminescence, fluorescence or spectrophotometric detection.

Claim 62: the nematode worms are wild type mutant, transgenic or humanized *C. elegans.*

Claim 80: the soluble concentration of water-soluble polymer in the liquid medium is 0.3%.

According to the Examiner the primary reference, Avery, teaches an assay that allows measurement of the pharynx-pumping rate in a population of worms suspended in a liquid

medium by measuring their uptake of iron particles. The Examiner asserts that Avery also teaches that the assay is useful for measuring the effects of drugs on pumping, and that wild-type worms and hermaphrodites can be used in the assay. The Examiner acknowledges that Avery does not teach a method of identifying a chemical substance, which has potential pharmacological activity using nematode worms, which method comprises the step of detecting a signal comprises detecting a biochemical changes in the nematode worms using non-visual detection means, wherein the non visual detection means is a FANS device. The deficiencies of the primary reference are not cured by the teaching of the secondary reference or by applicants' alleged admissions regarding a commercially available non-visual detection system.

The Examiner interprets Miwa as suggesting that the "chemical industry is producing novel chemical substance and research is being done to find new applications for known chemical substances and that in each case, it is desirable to establish a rapid method for testing substances" (Paper mailed 2/14/02, page 12). The Examiner asserts that one of ordinary skill in the art would combine the teaching of Avery with Miwa and would then view those teachings in combination with the existence of a commercially available non-visual detection system, and would arrive at the claimed invention.

Applicants reiterate the description of the primary reference, Avery, as described above in reference to the rejection of claims under 102(b) and 103(a). Avery does not teach dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means, which would include a FANS device. The deficiencies in the primary reference are not cured by the secondary reference, or by applicants' alleged admission of the existence of a non-visual detection device.

The secondary reference, Miwa, suggests that a rapid method of testing toxicity of substances is desirable and teaches that their method is such a rapid method. Thus, there is no motivation to modify the Miwa teachings in the manner suggested by the Examiner. Miwa teaches a method of assessing chemical effects on nematodes that involves contacting a nematode with a chemical and assessing the effect of the chemical by visual examination of a subsequent generation of nematodes. The reference does not teach detection using any non-visual detection means, does not teach placing equal numbers of nematodes in each well of a

multi-well plate, and does not teach or suggest methods to detect a signal *in the* nematode(s) contacted with the chemical.

To establish a *prima facie* showing of obviousness requires motivation, a reasonable expectation of success, and the prior art reference (or combination of references) must teach or suggest all the claimed limitations. The combination of the Avery and Miwa references, in view of the existence of a non-visual detection device (for example a FANS device), does not meet these requirements because when taken together the references do not provide motivation, teach, or suggest all the claimed limitations of the invention. There is no teaching in either Avery or Miwa that is directed to detecting a signal using a non-visual detection means. Avery teaches visual observation via hand counting and dark-field microscopy, and Miwa does not teach detection of signals of any kind in the worms in the assay, but rather teaches visual observation of offspring of the assay worms. Neither reference teaches or suggests the use of any non-visual detection method, therefore the combination of the teaching in these references would not lead to the claimed invention and one would not be motivated, based on the combination of these references to utilize a non-visual detection method.

In addition, the Examiner's assertion that the teachings of Avery and Miwa in combination with the existence of a non-visual detection system would lead one of ordinary skill in the art to the instant invention, does not meet the evidentiary requirements for a *prima facie* case of obviousness. The fact that a piece of equipment for non-visual detection is commercially available, be it a plate reader or a FANS device, does not serve as evidence of motivation to combine two references that do not teach use of any non-visual detection systems. The Examiner has merely disclosed isolated elements of the claimed invention without a specific teaching of how to go about the claimed invention (Smithkline Diagnostics v. Helena Laboratories, 859 F.2d 878 (Fed. Cir 1988), which is an impermissible use of hindsight and does not support a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 23-30, 36-37, 39, 40, 42, 44, 51-54, 58-62, 74-78, 80, and 85 under 35 U.S.C. 103(a) as being unpatentable over Avery in view of Miwa, taken with applicants' alleged admission that a non-visual detection device is commercially available.

The Examiner has rejected claims 1, 8-11, 17-20, 23-30, 36, 37, 39, 44, 53-61, 85-87, and 91-97 under 35 U.S.C. 103(a) as being unpatentable over Kerr et al. taken with Miwa et al., in further view of applicants' own admission that a non-visual detection system is commercially available from UNION BIOMETRICA, INC. Applicants respectfully traverse the rejection.

Claims 1, 8-11, 17-20, 23-30, 36, 37, 39, 44, 53, 54, 58-61, 85-87, and 91, 92 and 94-97 are described above in reference to the rejection of claims under 102(b) and 103(a). Claims 55-57 represent further limitations to claim 44, and claim 93 represents a further limitation to claim 86 as follows:

Claim 55: the marker molecule is capable of being cleaved by the addition of an enzyme present in the gut of the nematode worm to generate a fluorescent molecule, a luminescent molecule or a colored molecule.

Claim 56: the marker molecule is calcein-AM, BCECF-AM, fluorescein diphosphate (FDP), fluorescein diacetate (FDA), CMB-leu, AMPPD or X-gluc.

Claim 57: the marker molecule is sensitive to changes in pH.

Claim 93: the non-visual detection means is a FANS device.

According to the Examiner, Kerr teaches imaging calcium transients in a subset of excitable cells in *C. elegans*, and does not "teach a method of identifying a chemical substance, which has potential pharmacological activity using nematodes worms placed in equal numbers in multi-well plates, which method comprises the step of detecting a signal indicating a biochemical change using non-visual detection device, multi-well plates and a liquid medium or agar medium" (Paper mailed 2/14/02, page 10).

According to the Examiner Miwa suggests that the "chemical industry is producing novel chemical substance and research is being done to find new applications for known chemical substances and that in each case, it is desirable to establish a rapid method for testing substances" (Paper mailed 2/14/02, page 12). The Examiner asserts that one of ordinary skill in the art would combine the teaching of Kerr with Miwa and would then view those teachings in combination

with the existence of a commercially available non-visual detection system, and would arrive at the claimed invention.

Applicants reiterate the description of the primary reference, Kerr, as described above in reference to the rejection of claims under 102(b) and 103(a). The primary reference, Kerr, et al., is directed to methods for assessing electrical activity in *C. elegans* using genetically-encoded ratiometric fluorescent calcium sensors, which are visualized with two-photon confocal microscopy. Although the fluorescent calcium sensors are used to detect changes in the intracellular levels of ions, Kerr does not teach the use of any non-visual detection means to examine the electrical activity in the worms, or to examine phenotypic, physiological, behavioral, or biochemical changes in the nematode worms. Kerr also does not teach dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well plate. The teaching in the secondary references does not cure the deficiencies in the teachings of the Kerr reference.

Applicants reiterate the description of the secondary reference, Miwa, as described above in reference to the rejection of claims under 102(b) and 103(a). Miwa suggests that a rapid method of testing toxicity of substances is desirable and teaches that the method taught in Miwa is such a rapid method. Thus, there is no motivation to modify the Miwa teachings in the manner suggested by the Examiner. Miwa teaches a method of assessing chemical effects on nematodes that involves contacting a nematode with a chemical and assessing the effect of the chemical by visual examination of a subsequent generation of nematodes. The reference does not teach detection using any non-visual detection means, does not teach placing equal numbers of nematodes in each well of a multi-well plate, and does not teach or suggest methods to detect a signal *in* the nematode(s) contacted with the chemical.

To establish a *prima facie* showing of obviousness requires motivation, a reasonable expectation of success, and the prior art reference (or combination of references) must teach or suggest all the claimed limitations. The combination of the Kerr and Miwa references, in view of the existence of a non-visual detection device (e.g., a plate reader or a FANS device), does not meet these requirements because together the references do not provide motivation, teach, or suggest all the claimed limitations of the invention. There is no teaching in either Kerr or Miwa that is directed to detecting a signal using a non-visual detection means. Kerr teaches visual observation via confocal microscopy, and Miwa does not teach detection of signals of any kind

in the worms in the assay, but rather teaches visual observation of offspring of the assay worms. Neither reference teaches or suggests the use of any non-visual detection method, therefore the combination of the teaching in these references would not lead to the claimed invention and one would not be motivated, based on the combination of these references to utilize a non-visual detection method.

In addition, the Examiner's assertion that the teachings of Kerr and Miwa in combination with the existence of a non-visual detection system would lead one of ordinary skill in the art to the instant invention, does not meet the evidentiary requirements for a *prima facie* case of obviousness. The fact that a piece of equipment for non-visual detection is commercially available, (be it a plate reader or a FANS device), does not serve as evidence of motivation to combine two references that do not teach use of any non-visual detection systems. The Examiner has merely disclosed isolated elements of the claimed invention without a specific teaching of how to go about the claimed invention (Smithkline Diagnostics v. Helena Laboratories, 859 F.2d 878 (Fed. Cir 1988), which is an impermissible use of hindsight and does not support a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 8-11, 17-20, 23-30, 36, 37, 39, 44, 53-61, 85-87, and 91-97 under 35 U.S.C. 103(a) as being unpatentable over Kerr in view of Miwa, taken with applicants' alleged admission that a non-visual detection device (e.g. a plate reader or a FANS device) is commercially available.

The Examiner has rejected claims 1, 44, 51-59, 74-78, 80, and 85 under 35 U.S.C. 103(a) as being unpatentable over Avery taken with Miwa et al., in further view of applicants' own admission that a non-visual detection system is commercially available from UNION BIOMETRICA, INC., taken with any Mysore et al (Mol. Plant Microb. Interact. Vol. 11, abstract, 1998), Obexer et al., (Trop Med. Parasitol. Vol. 46, abstract, 1995), Denham (Cytometry, Vol. 19, abstract, 1996) Huan et al. (J. Immunol. Methods, Vol. 149, abstract, 1992), Yang et al., (Cell Transplant, Vol. 7, abstract, 1998), and Stevens et al., (Mol. Cell. Probes, Vol. 10, abstract, 1996). Applicants respectfully traverse the rejection.

Claims 1, 44, 51-59, 74-78, 80, and 85 are described above in reference to the rejection of claims under 102(b) and 103(a).

According to the Examiner the primary reference, Avery, teaches an assay that allows measurement of the pharynx-pumping rate in a population of worms suspended in a liquid medium by measuring their uptake of iron particles. The Examiner asserts that Avery also teaches that the assay is useful for measuring the effects of drugs on pumping, and that wild-type worms and hermaphrodites can be used in the assay. The Examiner acknowledges that Avery does not teach a method of identifying a chemical substance, which has potential pharmacological activity using nematode worms, which method comprises the step of detecting a signal comprises detecting a biochemical changes in the nematode worms using non-visual detection means, wherein the non visual detection means is a FANS device. The deficiencies of the primary reference are not cured by the teaching of the secondary reference or by applicants' alleged admissions regarding a commercially available non-visual detection system.

According to the Examiner Miwa suggests that the "chemical industry is producing novel chemical substance and research is being done to find new applications for known chemical substances and that in each case, it is desirable to establish a rapid method for testing substances" (Paper mailed 2/14/02, page 12).

The Examiner states that Avery taken with Miwa in further view of applicants' own admissions do not specifically teach the specific markers consisting of a calcein-AM, BCECF-AM, FDP, FDA, AMPPD, or X-gluc, but that because these fluorescent, luminescent, or colored markers were known in the art, it would have been *prima facie* obvious to combine the teaching of Avery with Miwa with the applicants' alleged admission of the existence of a commercially available non-visual detection system, in view of the markers, to create the claimed invention.

Applicants reiterate the description of the primary reference, Avery, as described above in reference to the rejection of claims under 102(b) and 103(a). Avery does not teach the use of dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate and does not teach detecting a signal indicating phenotypic, physiological, behavioral, or biochemical changes in the nematode worms using non-visual detection means, which would include a FANS device. The deficiencies in the primary reference are not cured by the secondary reference, applicants' alleged admission of the existence of a non-visual detection device, or by the existence of fluorescent, luminescent, or colored markers.

As iterated above, the secondary reference, Miwa, suggests that a rapid method of testing toxicity of substances is desirable and teaches that their method is such a rapid method. Thus,

there is no motivation to modify the Miwa teachings in the manner suggested by the Examiner. Miwa teaches a method of assessing chemical effects on nematodes that involves contacting a nematode with a chemical and assessing the effect of the chemical by visual examination of a subsequent generation of nematodes. The reference does not teach detection using any non-visual detection means, does not teach placing equal numbers of nematodes in each well of a multi-well plate, and does not teach or suggest methods to detect a signal *in* the nematode(s) contacted with the chemical.

To establish a *prima facie* showing of obviousness requires motivation, a reasonable expectation of success, and the prior art reference (or combination of references) must teach or suggest all the claimed limitations. The combination of the Avery and Miwa references, in view of the existence of a non-visual detection device (for example a FANS device), does not meet these requirements because together the references do not provide motivation, teach, or suggest all the claimed limitations of the invention. There is no teaching in either Avery or Miwa that is directed to detecting a signal using a non-visual detection means. Avery teaches visual observation via hand counting and dark-field microscopy, and Miwa does not teach detection of signals of any kind in the worms in the assay, but rather teaches visual observation of offspring of the assay worms. Neither reference teaches or suggests the use of any non-visual detection method, therefore the combination of the teaching in these references would not lead to the claimed invention and one would not be motivated, based on the combination of these references to utilize a non-visual detection method.

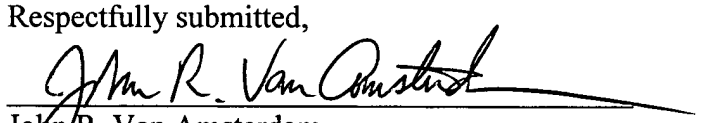
In addition, the Examiner's assertion that the teachings of Avery and Miwa in combination with the existence of a non-visual detection system, further combined with the knowledge in the art that fluorescent, luminescent, or colored markers existed, would lead one of ordinary skill in the art to the instant invention, does not meet the evidentiary requirements for a *prima facie* case of obviousness. The fact that a piece of equipment for non-visual detection is commercially available, be it a plate reader or a FANS device, does not serve as evidence of motivation to combine two references that do not teach use of any non-visual detection systems. In addition, the existence of various markers does not teach or suggest the use of the markers as taught in the claimed invention. The Examiner has merely disclosed isolated elements of the claimed invention without a specific teaching of how to go about the claimed invention

(Smithkline Diagnostics v. Helena Laboratories, 859 F.2d 878 (Fed. Cir 1988), which is an impermissible use of hindsight and does not support a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 44, 51-59, 74-78, 80, and 85 under 35 U.S.C. 103(a) as being unpatentable over Avery in view of Miwa, taken with applicants' alleged admission that a non-visual detection device is commercially available, taken with any Mysore et al (Mol. Plan. Microb. Interact. Vol. 11, abstract, 1998), Obexer et al., (Trop Med. Parasitol. Vol. 46, abstract, 1995), Denham (Cytometry, Vol. 19, abstract, 1996) Huan et al. (J. Immunol. Methods, Vol. 149, abstract, 1992), Yang et al., (Cell Transplant, Vol. 7, abstract, 1998), and Stevens et al., (Mol. Cell. Probes, Vol. 10, abstract, 1996).

In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejections and act favorably upon the claims. If the Examiner requires clarification for any aspect of this response, or if prosecution can be expedited for any other reason, Applicants respectfully request that the Examiner contact the undersigned by telephone.

Respectfully submitted,



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X07/14/02

Marked-up Claims

1. A method of identifying chemical substances which have potential pharmacological activity using nematode worms, which method comprises the steps of:

(a) dispensing substantially equal numbers of nematode worms into each of the wells of a multi-well assay plate;

(b) contacting the nematode worms with a chemical substance;

(c) detecting a signal indicating phenotypic, physiological, behavio[u]ral, or biochemical changes in the nematode worms using non-visual detection means.

8. (Twice Amended) The[A] method as claimed in claim 1 wherein the nematode worms are microscopic nematodes.

9. (Amended) The[A] method as claimed in claim 8 wherein the nematode worms are *C. elegans* or *C. briggsae.*

10. (Thrice Amended) The[A] method as claimed in [any one of]claim 1 wherein the step of detecting a signal comprises detecting a change in a measurable property of a marker molecule, whereby a change in the property of the marker molecule indicates a phenotypic, physiological, behavio[u]ral, or biochemical change in the nematode worms.

11. (Amended) The[A] method as claimed in claim 10 wherein the marker molecule is a fluorescent molecule, a luminescent molecule, or a coloured molecule.

12. (Amended) The[A] method as claimed in claim 10 wherein the marker molecule is a precursor of a fluorescent molecule, a precursor of a luminescent molecule, or a precursor of a coloured molecule.

13. (Amended) The[A] method as claimed in claim 12 wherein said marker molecule is capable of being cleaved by the action of an enzyme present in the gut of *C. elegans* to generate a fluorescent molecule, a luminescent molecule, or a coloured molecule.

17. (Thrice Amended) The[A] method as claimed in claim 1 wherein the non-visual detection means is a multi-well plate reader.

18. (Amended) The[A] method as claimed in claim 17 wherein the multi-well plate reader performs luminescence, fluorescence, or spectrophotometric detection.

19. (Thrice Amended) The[A] method as claimed in claim 1 wherein the non-visual detection means is a fluorescence activated nematode screening and sorting (FANS) device.

20. (Amended) The[A] method as claimed in claim 19 wherein the FANS device performs luminescence, fluorescence, or spectrophotometric detection.

23. (Thrice Amended) The[A] method as claimed in claim 1 wherein step (a) comprises dispensing substantially equal volumes of a homogeneous suspension of nematode worms into each of the wells of the multi-well assay plate.

24. (Amended) The[A] method as claimed in claim 23 wherein the homogeneous suspension comprises a suspension of *C. elegans* in a viscous solution.

25. (Amended) The[A] method as claimed in claim 24 wherein the viscous solution comprises a solution of a polymer material.

26. (Amended) The[A] method as claimed in claim 25 wherein the polymer material is low melting point agarose.

27. (Thrice Amended) The[A] method as claimed in claim 1 wherein the nematode worms are synchronized in the same growth stage.

28. (Amended) The[A] method as claimed in claim 27 wherein the nematode worms are eggs, L1 stage, L2 stage, L3 stage, L4 stage, adult worms, or dauer worms.

29. (Twice Amended) The[A] method as claimed in claim 27 wherein the worms are hermaphrodites or males.

30. (Thrice Amended) The[A] method as claimed in claim 1 wherein the nematode worms are a wild type strain, a mutant strain, a transgenic strain, or a humanized strain.

36. (Thrice Amended) The[A] method as claimed in claim 1 wherein step (a)[the method] is performed in a multi-well plate with liquid assay medium containing a water soluble polymer at a concentration sufficient to increase the viscosity of the medium.

37. (Amended) The[A] method as claimed in claim 36 wherein the water soluble polymer is carboxymethyl cellulose, low melting point agarose, or polyethylene glycol.

38. (Amended) The[A] method as claimed in claim 37 wherein the water soluble polymer is medium viscosity carboxymethyl cellulose.

39. (Twice Amended) The[A] method as claimed in claim 36 wherein the concentration of water soluble polymer in the liquid medium is 0.3%.

40. (Thrice Amended) The[A] method as claimed in claim 1 wherein step (a)[the method] is performed in a multi-well plate with liquid assay medium containing a water soluble polymer at a concentration sufficient to prevent the nematode worms from sticking to the wells of the multi-well plate.

41. (Twice Amended) The[A] method as claimed in claim 40 wherein the water soluble polymer is polethylene glycol, polyvinyl alcohol, or polyvinylpyrrolidone.

42. (Twice Amended) The[A] method as claimed in claim 40 wherein the concentration of water soluble polymer in the liquid medium is from 0.01% to 10%.

43. (Amended) The[A] method as claimed in claim 42 wherein the concentration of water soluble polymer in the liquid medium is 0.1%.